

(19) World Intellectual Property  
Organization  
International Bureau



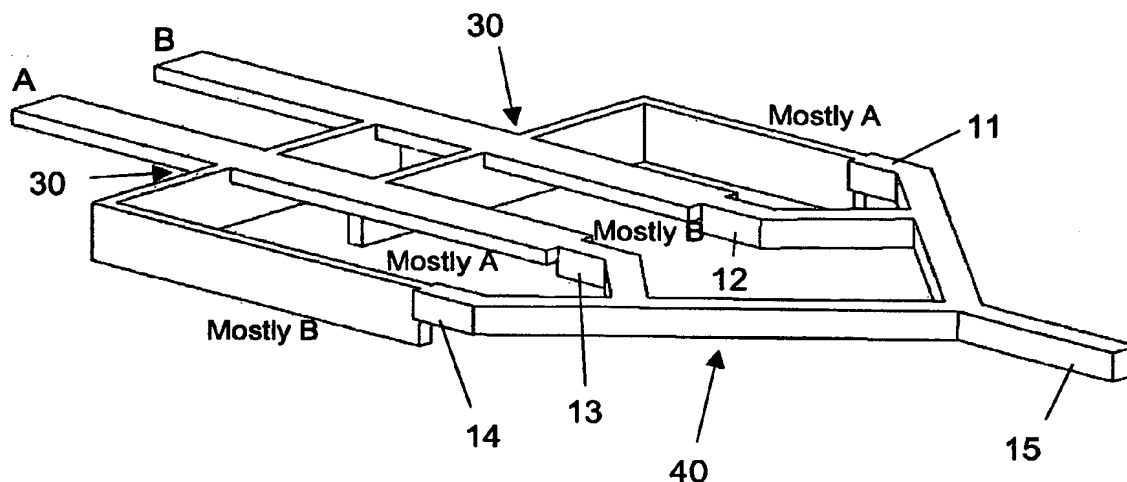
(43) International Publication Date  
8 April 2004 (08.04.2004)

PCT

(10) International Publication Number  
**WO 2004/028954 A1**

- (51) International Patent Classification<sup>7</sup>: **B81B 1/00**, (74) Agent: GILL JENNINGS & EVERY; Broadgate House, 7 Eldon Street, London EC2M 7LH (GB).  
B01L 3/00, B01F 13/00
- (21) International Application Number: PCT/GB2003/004045
- (22) International Filing Date: 23 September 2003 (23.09.2003)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data: 02256607.9 24 September 2002 (24.09.2002) EP
- (71) Applicant (for all designated States except US): **THE TECHNOLOGY PARTNERSHIP PLC** [GB/GB]; Melbourne Science Park, Cambridge Road, Melbourn, Royston, Hertfordshire SG8 6EE (GB).
- (72) Inventor; and
- (75) Inventor/Applicant (for US only): **SOMERVILLE, John, Matthew** [GB/GB]; 28 Cambridge Crescent, Bassingbourn, Nr. Royston, Hertfordshire SG8 5LP (GB).
- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Published:  
— with international search report
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: FLUID ROUTING DEVICE



(57) Abstract: A single layer microfluidic fluid routing device comprising: a first channel having a cross-section of a first aspect ratio and a first depth and having a longitudinal axis; and a second channel having a second cross-section of a different aspect ratio and a second different depth; wherein the second channel passes through at least part of the first channel in a direction transverse to the longitudinal axis.

## FLUID ROUTING DEVICE

This invention relates to a single layer fluid routing device and a method of routing fluid within a single layer. The invention relates, in particular, to a fluid routing device and method which can be utilised to mix two or more fluids, preferably in a microfluidic circuit. Although described with reference to microfluidic circuits, the present invention can be equally applied outside of the area, for example in oil pipelines or other fluid networks.

Microfluidic networks, such as those used in so-called "lab on a chip" systems are increasingly common and it is often necessary to mix two or more fluids which are passing within such a microfluidic network, for example, to enable a reaction to take place or to allow one fluid to be diluted by mixing with a different fluid. In such microfluidic networks, the fluid flow is generally laminar and therefore the amount by which the fluids are mixed is limited by the rate of diffusion of the two fluids, which is proportional to the size of the surface area of contact between the fluids.

Mixing two or more fluids with a single interface in a diffusion limited regime is therefore very slow and requires large dead volumes within the network of passages. Consequently, it is necessary to try to maximise the surface area between the fluids to be mixed, and so increase the rate of diffusion.

Typically this is achieved by combining two sets of interlaced channels in each of which a pair of different fluids flows, as shown in Figure 1, so that a multilayered laminate flow is formed, thereby enabling quicker mixing of the fluids. Figure 1 shows a simple mixing device 10 having fluid supply channels 11, 12, 13, 14. Channels 11 and 13 supply fluid A and channels 12 and 14 supply fluid B. The four channels are combined to form a four layered laminate flow 15 which has three interfaces between fluid A and fluid B. The increase in the number of interfaces increases the amount of diffusion between the different fluids and therefore reduces the time required for thorough mixing to occur.

Unfortunately, in this form of interdigitated laminar mixing, all the channels 11, 12, 13, 14 have to be connected to individual reservoirs of either fluid A or fluid B to enable this device to be produced within a single microfluidic layer. However, having multiple reservoirs for the same fluid is an inefficient use of space within the device. Therefore, in order to use only a single reservoir for each fluid A and B, a two layered device is desirable.

One example of a simple two layered mixing device 20 is shown in Figure 2, in which passageways 21 and 22, containing fluid A and B respectively, are brought together in a single passage which is then split into upper 23 and lower 24 pathways, thereby creating the two layers within the device, and which are then brought back together as a four layered laminate flow 25, similar to that produced by the device of Figure 1.

There are several disadvantages to a two layered construction and these include a greater manufacturing cost due to the need for multiple layers to be shaped and significant manufacturing complexity in aligning the separate layers, typically to micron scale accuracy, which also significantly increases the cost of an individual device.

- 5 Multilayer systems are also often difficult to prime repeatedly at low pressures and at low flow rates and this leads to incorrect, or at least unreliable, test results.

As cost is a primary parameter in the commercial viability of microchemistry or "lab on a chip" microfluidic circuits, it is an aim of the present invention to provide a fluid routing device using only a single layer, but which does not unduly limit the routing of fluid within the device and hence reduce the function that can be achieved by such a device.

According to the present invention, there is provided a single layer microfluidic fluid routing device comprising:

- a first channel having a cross-section of a first aspect ratio and a first depth;
- a second channel having a second cross-section of a second different aspect ratio
- 15 and a second different depth;

wherein the second channel intersects with the first channel from a first point to a second point, the first and second points having different offsets relative to the cross-section of the first channel.

Thus, the present invention provides a device which is capable of moving part of one or more fluids from one position in a flow to a different position in the flow to enhance mixing of the fluids. The device is space efficient as it does not require lengthy passageways in which the diffusion takes place as the flow pathways are relatively short compared to other known devices and therefore means that the mixing is carried out quickly.

25 When the depths of the channels are equal, the network is pseudo two dimensional and there will generally be little or no crossing of the two flows. However, as the depths of the channel are caused to differ, partial crossing of the flows starts to occur. In many cases, it is desirable to have similar viscous drag on the two fluid flows and so the two channels have opposite aspect ratios; for example 2:1 and 1:2.

30 As the aspect ratios become more elongated, more complete crossover of the two fluid flows is seen. However the channels become increasingly expensive to fabricate and the viscous drag rapidly increases. Taking these considerations into account, aspect ratios in the range between 1.5:1 and 10:1 are suitable, while aspect ratios in the region of 3:1 to 6:1 are the more preferred.

35 The present invention also provides a single layer microfluidic fluid routing device comprising:

a first channel having a cross-section of a first aspect ratio and a first depth and having a longitudinal axis; and

a second channel having a cross-section of a second different aspect ratio and a second different depth,

- 5        wherein the second channel passes through at least part of the first channel in a direction transverse to the longitudinal axis.

The cross-section of the intersecting first and second channels may be T-shaped. The first and second channels may be elongate in cross-section typically having an aspect ratio of 5.

- 10       The aspect ratio of the first channel may be a 90° rotation of the aspect ratio of the second channel to equalise the flow through each channel and the first and second channels preferably have substantially the same cross-sectional area.

The total cross-sectional area of the first and second channels is preferably also substantially constant.

- 15       The second channel may be separate from the first channel until the first point. The second channel may continue beyond the first channel after the second point. Alternatively, the second channel may extend only between the first and the second point.

- In an example in which the second channel continues beyond the first channel after the second point, the first and second channels may be recombined to create a multi-laminar flow. In this example, the first and second channels may pass through a  
20       respective intermediary channel prior to recombination, each intermediary combination having substantially the same aspect ratio cross-section.

- The second channel may be formed by a gradual change in aspect ratio from the first point. Alternatively, at the first point, there may be a step which signifies the start of  
25       the second channel.

At the second point, there may be a step which indicates the end of the second channel.

The first and second channels may have flow directions which are at 90° to each other.

- 30       The first and second points may be at different longitudinal positions in the first channel, each intermediary channel having the same aspect ratio cross-section.

The invention also provides a fluid mixer comprising a fluid routing device as described above and fluid supply means for supplying the fluids supply to be mixed and which is connected to the fluid routing device.

- 35       The mixer preferably comprises additional fluid routing devices as described above connected in series, such that an outlet from one device passes into the inlet of a subsequent device.

The fluid mixer may comprise a pair of inlet passages for supplying, in use, different fluids to the first channel. Alternatively, there may be three inlet passages, the outer two supplying a different fluid to the central passage. This is particularly advantageous if the volume of the fluid supplied by the central passage is small compared to the volume of the other fluid, as it increases the number of interfaces even before the fluids enter the routing device itself.

The mixer may additionally comprise a geometric pin between each of the fluid supply passages and the first channel.

According to a second aspect of the present invention, there is also provided a method of routing fluid in a single layer, the method comprising the steps of;

providing a fluid in a first channel having a cross-section of a first aspect ratio;

passing a portion of the fluid from the first channel into a second channel which has a cross-section of a second different aspect ratio and which intersects with the first channel from a first point to a second point, each point having a different offset relative to the cross-section of the first channel; and

moving the fluid through the second channel from the first point to the second point.

The method preferably comprises the further step of recombining the fluid from the second channel into a different portion of the fluid in the first channel.

The method may also comprise the step of passing the fluids from the first and the second channels into respective intermediary channels, each of which may have the same aspect ratio cross-section, prior to recombining the fluids from the first and the second channels.

There is also provided a method of routing fluid in a single layer, the method comprising the steps of:

providing a first fluid in a first channel having a cross-section of a first aspect ratio; and

flowing a second fluid, within a second channel having a cross-section of a second aspect ratio and intersecting the first channel, across the first channel.

There is also provided a method of diverting fluid from a first channel to a second channel, the method comprising the step of flowing a fluid through a fluid routing device as described above.

Examples of the present invention will now be described with reference to the accompanying drawings, in which:

Figure 1 is a schematic perspective view of an example of a prior art mixer;

Figure 2 is a schematic perspective view of another example of a prior art mixer;

Figure 3 is a schematic perspective view of one example of a fluid routing device according to the present invention;

Figure 4 is a schematic perspective view of a fluid mixer using the fluid routing device of Figure 3;

5        Figure 5 is a schematic perspective view of another example of a fluid routing device according to the present invention;

Figure 6 is a series of cross-sections through the fluid routing device of Figure 5;

Figure 7 is a schematic plan view of the mixer of Figure 5;

10       Figure 8 is a plan view of a fluid mixer using a plurality of units shown in Figures 5 and 7;

Figure 9 is one example of a meniscus pinning device for use in the present invention; and

Figure 10 is another example of a meniscus pinning device for use in the present invention.

15       Figure 3 shows a fluid routing device 30 having a first channel 31 and a second channel 32 which are arranged at substantially 90° to one another. Channel 31 carries fluid A and channel 32 carries fluid B. Channel 31 has a relatively wide shallow cross-section, whereas channel 32 has a narrow deep cross-section. Channel 32 passes through channel 31 such that, at the intersection 33, some but not significant, mixing  
20 occurs between fluid A and fluid B. Thus, outlet end 34 of channel 31 and outlet end 35 of the channel 32 contain mostly fluid A and fluid B respectively. This is a simple method of crossing two fluids over in a single layer, i.e. within the maximum depth of the deeper channel, and, as some cross contamination occurs at the intersection 33, it is most suited to use in a fluid mixer, an example of which is shown in Figure 4, where this will be  
25 beneficial.

As can be seen in Figure 4, a fluid mixer 40 is provided using two of the fluid routers 30 shown in Figure 3 and which have been applied to the network of passages 11, 12, 13, 14 from Figure 1, via a 90° change in aspect ratio, to enable this construction to be formed from a single layer, thereby reducing the manufacturing costs, and the  
30 complexity of the design as only a single reservoir is required for each fluid A and B. In this way, a four layered laminate flow 15 is produced at the outlet of mixer 40.

A further example of a device according to the invention is shown in Figures 5, 6 and 7 in which a fluid mixing unit 50 includes supply passages 51, 52 which are combined at an intersection 53 to form an inlet passage 54. A wide, shallow first channel 55 extends  
35 from the inlet passage 54 and, at a first point 56, a narrow, deep second channel 57 is formed, in this example by a step change 58. The second channel 57 moves across the first channel 55 until, at a second point 59, it separates from the first channel 55.

The first and second channels are then fed into intermediary channels 60 which recombine to form a passageway 61, which contains a four way laminar flow as shown in Figure 6.

5 The length of passageway 61 will be dependent upon the fluids used and their flow rate. For example, passageway 61 may be shaped so that it becomes narrower and deeper than at the point at which the channels 60 merge.

Figure 6 shows the location of the different fluids supplied by passageways 51 and 52 at different cross-sections through the mixer 50 of Figure 5, and it will be appreciated that between first point 56 and second point 59, the first channel 55 and second channels  
10 57 intersect with each other.

The square cross-section inlet passage 54 transforms, at first point 56, via a step change 58, although this may be a gradual change, into a T-shaped cross-section. The vertical (second channel 57) and horizontal (first channel 55) components of the "T" bifurcate, with both the first channel and the second channel containing a portion of both  
15 fluid A and fluid B. The two separate channels can then be recombined, via intermediary channels 60, in channel 61 to give a laminate flow with three interfaces which would be expected to increase the rate of diffusion by the square number of the number of interfaces ( $n^2$ ); in this case  $n = 3$ .

Importantly, and as shown in Figure 8, plural mixing units 50 shown in Figure 5 can  
20 be provided in series, each approximately doubling the number of interfaces, thereby introducing an exponential relationship between the number of mixer units and the number of interfaces.

This creates a single-layer mixer which uses chip area efficiently, due to its exponential mixing nature and which, providing the flow regime is laminar, will operate at  
25 a wide range of flow rates and channel sizes.

As referred to earlier, priming parallel structures at very low flow rates can be problematic. The present invention is resistant to these problems due to its modular construction, but it is still desirable to improve the priming to make use of every unit in the chain, thereby minimising dead volume and chip area. Techniques such as CO<sub>2</sub> priming  
30 and the use of a surfactant to solve these problems are well known, but the introduction of extra chemical species to a fluid can be undesirable in sensitive chemical systems.

The use of a hydrophobic dot at the fluid recombination mode, i.e. the junction between passages 60 and 61, can be used to pin the fluids and ensure complete priming, but this can add considerably to the cost of the chip and is therefore also undesirable,  
35 given the considerable implications of increase cost described earlier.

Accordingly, simple geometric pins in the recombination mode are the simplest method of ensuring priming, and these can be easily manufactured as part of the fluidic

layer at negligible extra costs. Two possible geometries are shown in Figures 9 and 10 as examples. Both pins 70, 80 incorporate flow restrictions 71, 81 which pin the first fluid to reach the node until the second fluid arrives at the node. This occurs because, once fluid has reached the flow restriction in one passage, the fluid meniscus forms across the restriction, thereby increasing the resistance to flow. Thus, fluid will flow through the other of the passages, as it has no impediment to the flow, until its meniscus also reaches the flow restriction. At this time, one fluid breaks through one of the restrictions 71, 81 and begins flowing, and this will destroy the remaining pin, thereby ensuring both parallel arms of the structure are fully primed.

10 While geometric pins may be used to enhance the priming of parallel structures, there is still a problem regarding bubbles from elsewhere in the circuit becoming trapped within the mixer.

For example, when multiple fluids are brought together before mixing, they will be inevitably a timing difference between these fluids. This will often manifest itself in a bubble of trapped air which then be pushed into the fluidic circuit. Another source of bubbles may be the fluid reservoir if this is imperfectly degassed/primed.

20 A simple geometric bubble trap 90, as shown in figures 11 and 12, placed after the combination of fluids can be used to capture these bubbles and to prevent them from entering the fluidic circuit where they may cause blockages. A simple design compatible with a single fluidic layer is shown in Figures 11 and 12 and comprises an array of pillars 91 which offer many parallel paths from the entrance to the exit. In such a structure bubbles will become trapped in the voids 92, before entering the mixer via channel 54.



## CLAIMS

1. A single layer microfluidic fluid routing device comprising:  
a first channel having a cross-section of a first aspect ratio and a first depth;  
5 a second channel having a second cross-section of a second different aspect ratio  
and a second different depth;  
wherein the second channel intersects with the first channel from a first point to  
a second point, the first and second points having different offsets relative to the cross-  
section of the first channel.
- 10 2. A single layer microfluidic fluid routing device comprising:  
a first channel having a cross-section of a first aspect ratio and a first depth and  
having a longitudinal axis; and  
a second channel having a cross-section of a second different aspect ratio and a  
15 second different depth,  
wherein the second channel passes through at least part of the first channel in a  
direction transverse to the longitudinal axis.
- 20 3. A device according to either claim 1 or claim 2, wherein the cross-section of the  
intersecting first and second channels is T-shaped.
4. A device according to any one of the preceding claims, wherein the first and  
second channels are elongate in cross-section.
- 25 5. A device according to any one of the preceding claims, wherein the aspect ratio  
of the first channel is a 90° rotation of the aspect ratio of the second channel.
6. A device according to any one of the preceding claims, wherein the first and  
second channels have substantially the same cross-sectional area.
- 30 7. A device according to any one of the preceding claims, wherein the total cross-  
sectional area of the first and second channels is substantially constant.
8. A device according to claim 1, wherein the aspect ratios of the two channels are  
35 in the range between 1.5:1 and 10:1.

9. A device according to claim 8, wherein aspect ratios of the two channels are in the range between 3:1 and 6:1.
10. A device according to any one of the preceding claims, wherein the second channel is separate from the first channel until the first point.
11. A device according to any one of the preceding claims, wherein the second channel continues beyond the first channel after the second point.
12. A device according to any one of claims 1 to 9, wherein the second channel extends only between the first and the second point.
13. A device according to any one of the preceding claims, wherein the second channel is formed by a gradual change in aspect ratio from the first point.
14. A device according to any one of the claims 1 to 12, further comprising, at the first point, a step which signifies the start of the second channel.
15. A device according to any one of claims 1 to 11 and 13 and 14 when not dependent upon claim 10, further comprising, at the second point, a step which indicates the end of the second channel.
16. A device according to any one of the preceding claims, wherein the first and second channels have flow directions which are at 90° to each other.
17. A device according to any one of claims 1 to 13, wherein the first and second points are at different longitudinal positions in the first channel.
18. A fluid mixer comprising:  
a fluid routing device according to any one of the preceding claims;  
fluid supply means for supplying the fluids to be mixed and which is connected to the fluid routing device.
19. A device according to claim 18, wherein the first and second channels are recombined.

20. A device according to claim 19, wherein the first and second channels pass through a respective intermediary channel prior to recombination.
21. A device according to claim 20, wherein the intermediary channels have the same aspect ratio cross-section.
22. A mixer according to any one of claims 18 to 21, further comprising additional fluid routing devices according to any one of claims 1 to 17, connected in series.
23. A fluid mixer according to any one of claims 18 to 22, further comprising a pair of inlet passages for supplying, in use, different fluids to the first channel.
24. A fluid mixer according to claim 23, further comprising a geometric pin between each of the fluid supply passages and the first channel.
25. A method of routing fluid in a single layer, the method comprising the steps of:  
providing a fluid in a first channel having a cross-section of a first aspect ratio;  
passing a portion of the fluid from the first channel into a second channel which has a cross-section of a second different aspect ratio and which intersects with the first channel from a first point to a second point, each point having a different offset relative to the cross-section of the first channel; and  
moving the fluid through the second channel from the first point to the second point.
26. A method according to claim 25, further comprising the step of recombining the fluid from the second channel into a different portion of the fluid in the first channel.
27. A method according to either claim 25 or claim 26, further comprising the step of passing the fluid from the first and the second channel into respective intermediary channels, each of which has the same aspect ratio cross-section, prior to recombining the fluids from the first and the second channels.
28. A method of routing fluid in a single layer, the method comprising the steps of:  
providing a first fluid in a first channel having a cross-section of a first aspect ratio;  
and  
flowing a second fluid, within a second channel having a cross-section of a second aspect ratio and intersecting the first channel, across the first channel.

29. A method of diverting fluid from a first channel to a second channel, the method comprising the step of:  
flowing a fluid through a device according to any one of claims 1 to 17.

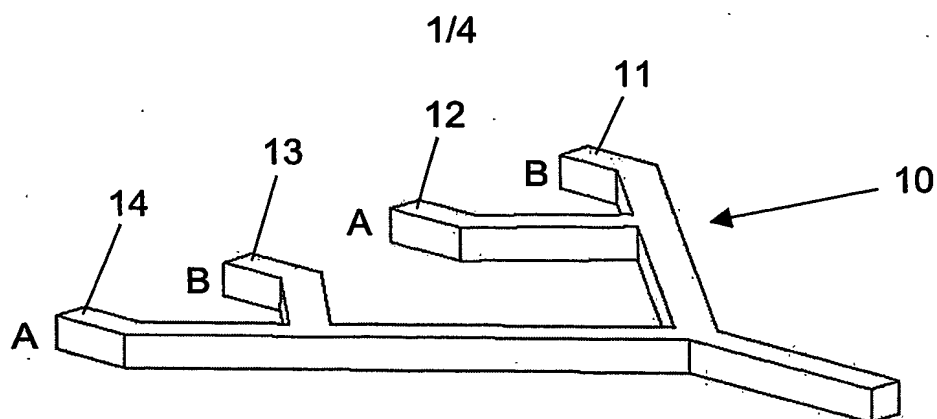


Figure 1

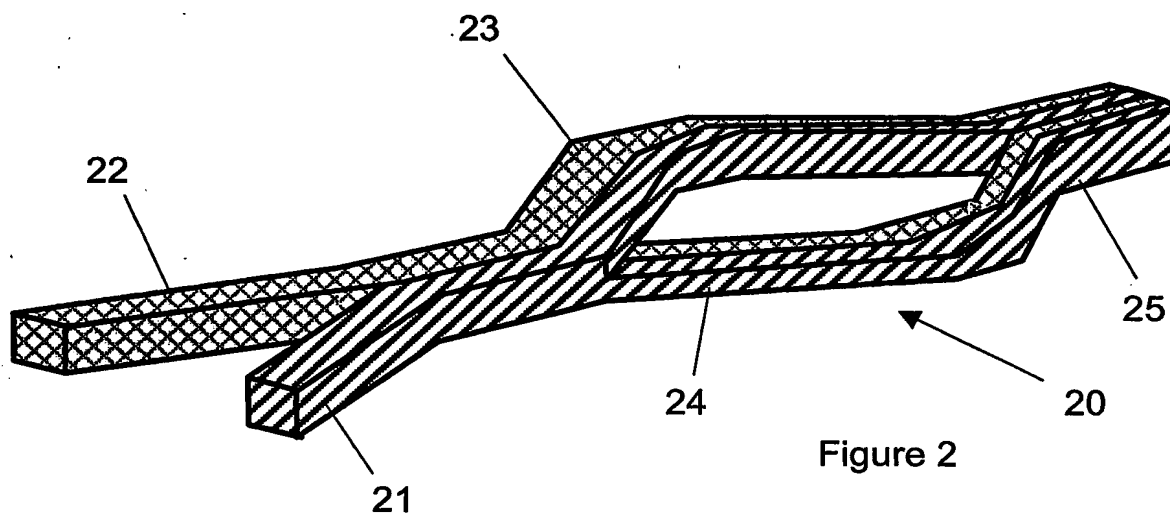


Figure 2

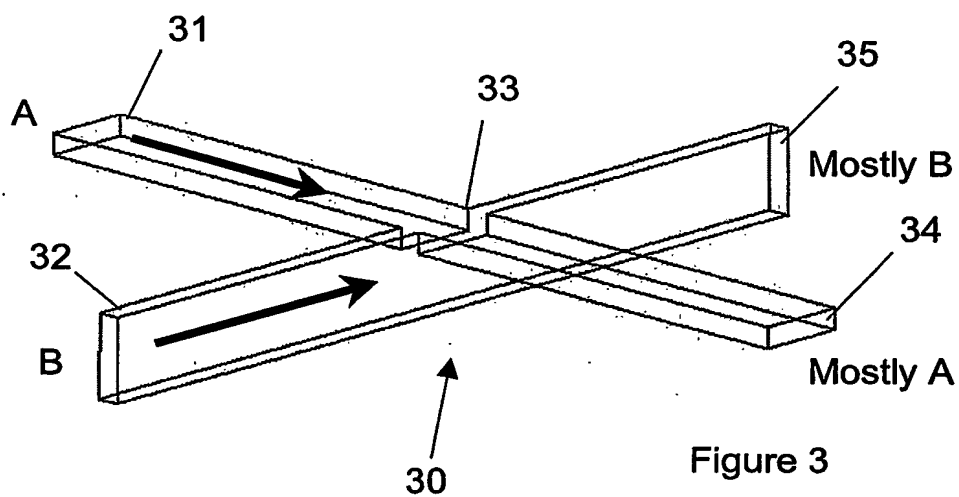


Figure 3

2/4

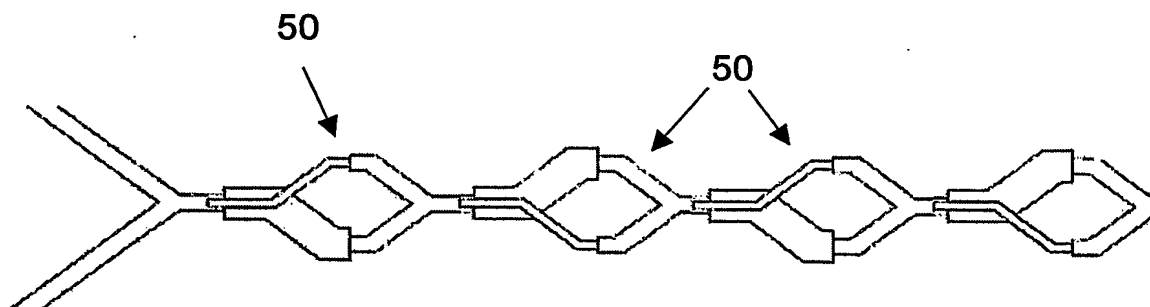
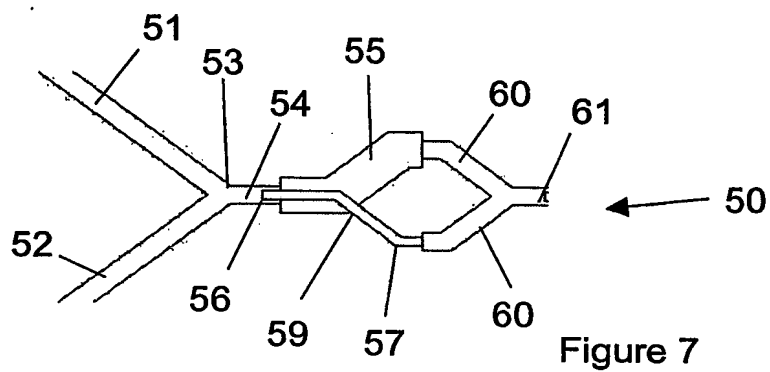
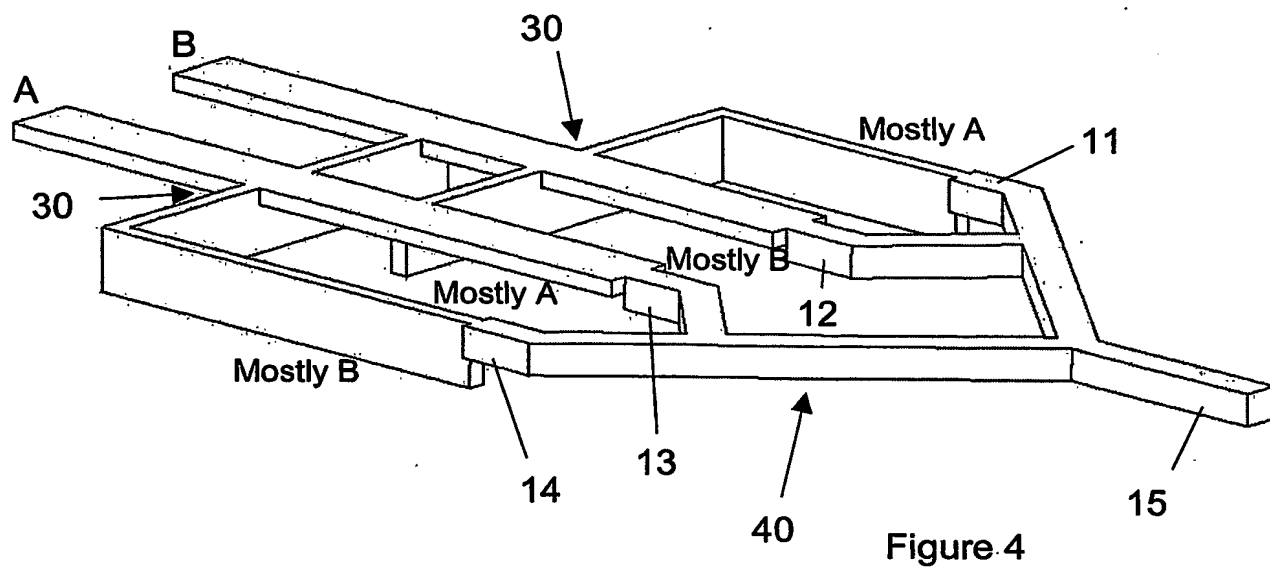
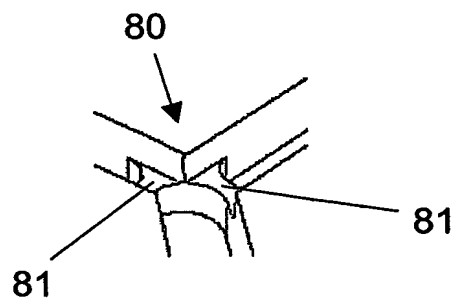
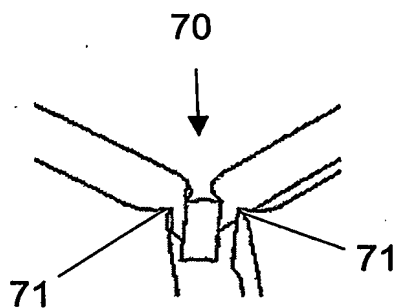
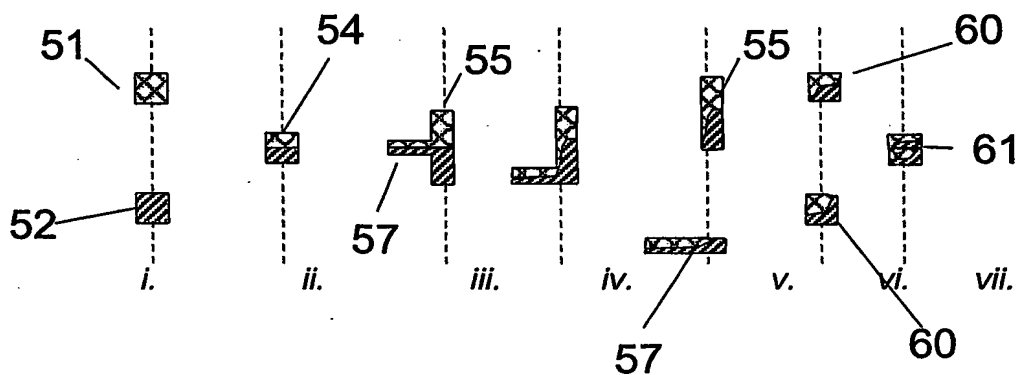
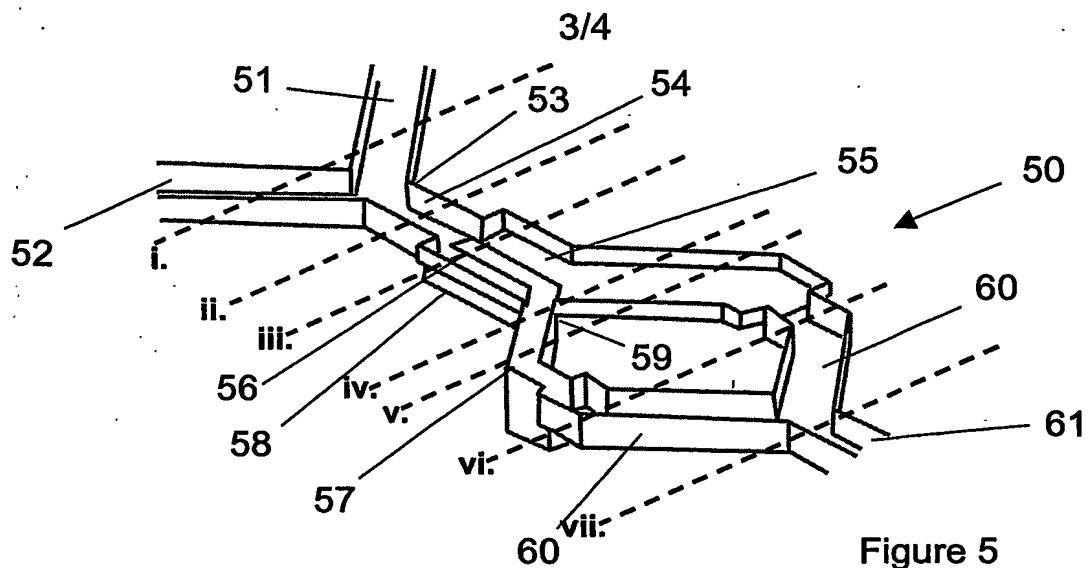


Figure 8



4/4

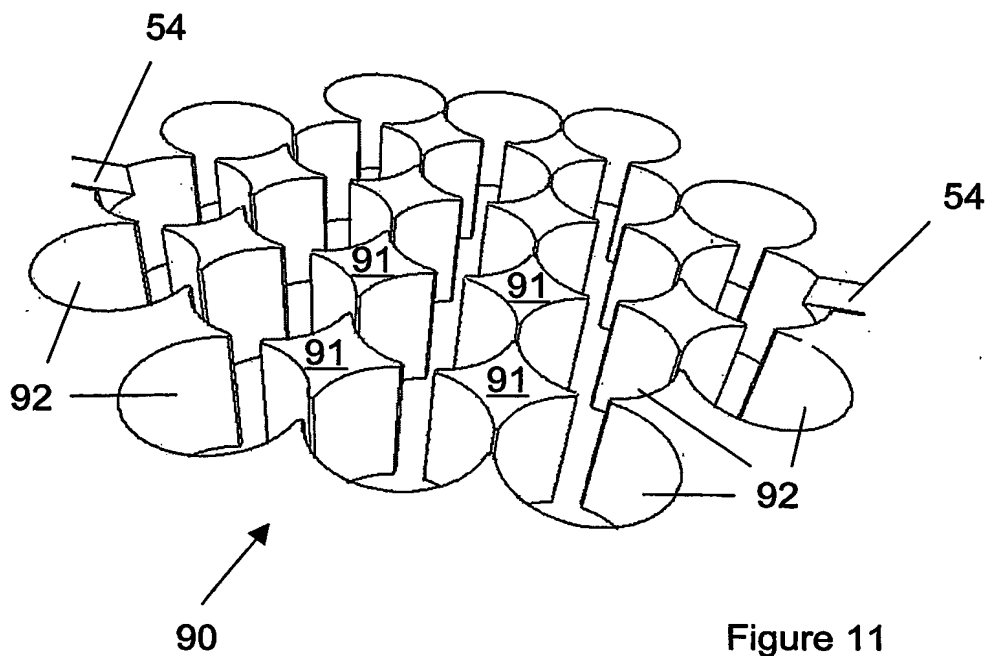


Figure 11

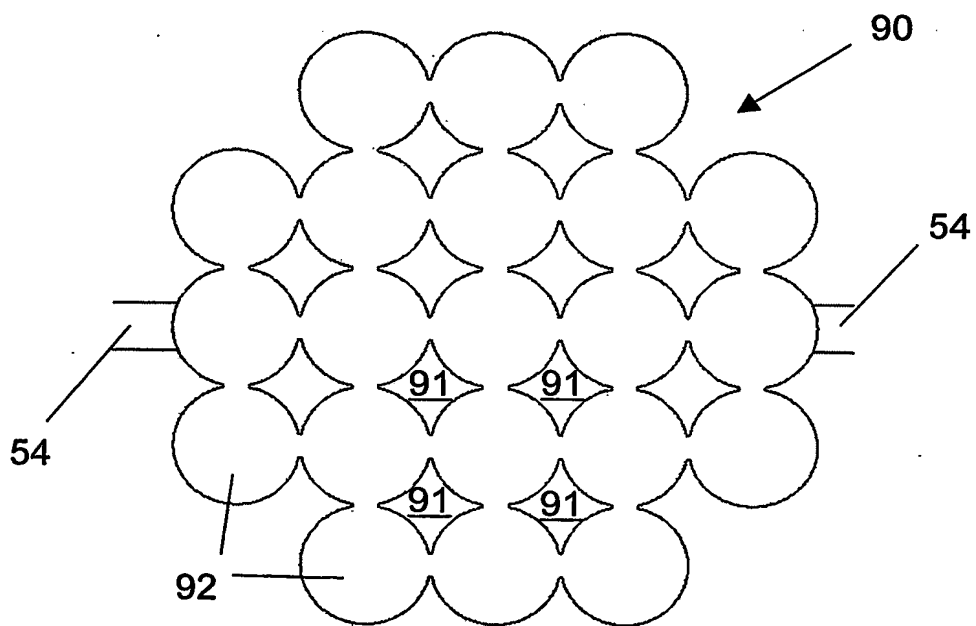


Figure 12



# INTERNATIONAL SEARCH REPORT

Internat Application No  
PCT/GB 03/04045

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 7 B81B1/00 B01L3/00 B01F13/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 7 B81B B01L B01F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, INSPEC, COMPENDEX

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X  A	WO 01 54784 A (MESOSYSTEMS TECHNOLOGY INC) 2 August 2001 (2001-08-02)  figures 1,5-7 page 3, line 4 -page 4, line 6 page 5, line 34 -page 9, line 12 page 11, line 28 -page 17, line 22	1,2,4, 8-11, 13-17, 25,28,29
X  A	US 5 948 684 A (HOLL MARK R ET AL) 7 September 1999 (1999-09-07) figures 1-5 column 21, line 12 -column 27, line 42	3,5-7, 12, 18-24, 26,27  25-28  1-24,29
	-/--	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents :

\*A\* document defining the general state of the art which is not considered to be of particular relevance

\*E\* earlier document but published on or after the international filing date

\*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

\*O\* document referring to an oral disclosure, use, exhibition or other means

\*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\*Z\* document member of the same patent family

Date of the actual completion of the international search

3 December 2003

Date of mailing of the international search report

19/12/2003

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3018

Authorized officer

Polesello, P

# INTERNATIONAL SEARCH REPORT

Intern: Application No  
PCT/GB 03/04045

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 6 136 272 A (WEIGL BERNHARD ET AL) 24 October 2000 (2000-10-24) figures 2-17 column 9, line 25 -column 17, line 65 -----	1-29
A	EP 1 065 378 A (CALIFORNIA INST OF TECHN) 3 January 2001 (2001-01-03) figures 1-18,23-35 paragraphs '0038!-'0067!, '0123!-'0131!, '0144!-'0184! -----	1-29

# INTERNATIONAL SEARCH REPORT

Internal Application No  
PCT/US 03/04045

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0154784	A	02-08-2001	US 6290065 B1 CA 2359702 A1 EP 1202822 A2 WO 0154784 A2 US 2002179499 A1 US 2002157993 A1	18-09-2001 02-08-2001 08-05-2002 02-08-2001 05-12-2002 31-10-2002
US 5948684	A	07-09-1999	US 5972710 A AU 5450498 A CA 2222815 A1 EP 1002227 A1 JP 2001511520 T WO 9905512 A1 US 6171865 B1 US 6582963 B1 US 2003211507 A1 US 6541213 B1 US 6454945 B1	26-10-1999 16-02-1999 25-01-1999 24-05-2000 14-08-2001 04-02-1999 09-01-2001 24-06-2003 13-11-2003 01-04-2003 24-09-2002
US 6136272	A	24-10-2000	NONE	
EP 1065378	A	03-01-2001	AT 215673 T AU 5773400 A BR 0011982 A CA 2378190 A1 CN 1369039 T DE 60000109 D1 DE 60000109 T2 DK 1065378 T3 EP 1065378 A2 EP 1194693 A2 EP 1195523 A2 ES 2174798 T3 GB 2352283 A JP 2003524738 T NO 20016268 A WO 0101025 A2 US 2003019833 A1 US 2001054778 A1 US 2001029983 A1 US 2001033796 A1 US 2002029814 A1 US 2002025529 A1 US 2002144738 A1 ZA 200110315 A	15-04-2002 31-01-2001 17-09-2002 04-01-2001 11-09-2002 08-05-2002 07-11-2002 29-07-2002 03-01-2001 10-04-2002 10-04-2002 16-11-2002 24-01-2001 19-08-2003 27-02-2002 04-01-2001 30-01-2003 27-12-2001 18-10-2001 25-10-2001 14-03-2002 28-02-2002 10-10-2002 17-12-2002